INTERNATIONAL EDITION
Not authorised for sale in North America and the Caribbean

Lippincott's Illustrated Reviews

Series Editor:
Richard A. Harvey

Biochemistry

5th edition

Richard Harvey
Denise Ferrier

Wolters Kluwer Health | Lippincott Williams & Wilkins

Lippincott's Illustrated Reviews: Biochemistry

Fifth Edition

Richard A. Harvey, PhD
Professor Emeritus
Department of Biochemistry
University of Medicine and Dentistry of New Jersey–
Robert Wood Johnson Medical School
Piscataway, New Jersey

Denise R. Ferrier, PhD
Professor
Department of Biochemistry and Molecular Biology
Drexel University College of Medicine
Philadelphia, Pennsylvania

Wolters Kluwer Health | Lippincott Williams & Wilkins

Philadelphia • Baltimore • New York • London
Buenos Aires • Hong Kong • Sydney • Tokyo

Acquisitions Editor: Susan Rhyner
Product Manager: Jennifer Verbiar
Designer: Holly Reid McLaughlin

351 West Camden Street
Baltimore, MD 21201

Two Commerce Square
2001 Market Street
Philadelphia, PA 19103

Printed in China

Library of Congress Cataloging-in-Publication Data

Harvey, Richard A., Ph. D.
Biochemistry / Richard A. Harvey, Denise R. Ferrier ; computer graphics, Michael Cooper. -- 5th ed.
p. cm.
Rev. ed. of: Biochemistry / Pamela C. Champe, Richard A. Harvey, Denise R. Ferrier. 4th ed. c2008.
Includes bibliographical references and index.
ISBN 978-1-60913-998-8 (alk. paper)
1. Biochemistry--Outlines, syllabi, etc. 2. Biochemistry--Examinations, questions, etc. 3. Clinical biochemistry--Outlines, syllabi, etc. 4. Clinical biochemistry--Examinations, questions, etc. I. Ferrier, Denise R. II. Title.
QP514.2.C48 2010
612'.015--dc22
2010008046

DISCLAIMER

Care has been taken to confirm the accuracy of the information present and to describe generally accepted practices. However, the authors, editors, and publisher are not responsible for errors or omissions or for any consequences from application of the information in this book and make no warranty, expressed or implied, with respect to the currency, completeness, or accuracy of the contents of the publication. Application of this information in a particular situation remains the professional responsibility of the practitioner; the clinical treatments described and recommended may not be considered absolute and universal recommendations.

The authors, editors, and publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accordance with the current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new or infrequently employed drug.

Some drugs and medical devices presented in this publication have Food and Drug Administration (FDA) clearance for limited use in restricted research settings. It is the responsibility of the health care provider to ascertain the FDA status of each drug or device planned for use in their clinical practice.

To purchase additional copies of this book, call our customer service department at **(800) 638-3030** or fax orders to **(301) 223-2320**. International customers should call **(301) 223-2300**.

Visit Lippincott Williams & Wilkins on the Internet: http://www.lww.com. Lippincott Williams & Wilkins customer service representatives are available from 8:30 am to 6:00 pm, EST.

RRS1003

Contents

UNIT I: Protein Structure and Function

Amino Acids 1

I. OVERVIEW

Proteins are the most abundant and functionally diverse molecules in living systems. Virtually every life process depends on this class of molecules. For example, enzymes and polypeptide hormones direct and regulate metabolism in the body, whereas contractile proteins in muscle permit movement. In bone, the protein collagen forms a framework for the deposition of calcium phosphate crystals, acting like the steel cables in reinforced concrete. In the bloodstream, proteins, such as hemoglobin and plasma albumin, shuttle molecules essential to life, whereas immunoglobulins fight infectious bacteria and viruses. In short, proteins display an incredible diversity of functions, yet all share the common structural feature of being linear polymers of amino acids. This chapter describes the properties of amino acids. Chapter 2 explores how these simple building blocks are joined to form proteins that have unique three-dimensional structures, making them capable of performing specific biologic functions.

II. STRUCTURE OF THE AMINO ACIDS

Although more than 300 different amino acids have been described in nature, only 20 are commonly found as constituents of mammalian proteins. [Note: These are the only amino acids that are coded for by DNA, the genetic material in the cell (see p. 395).] Each amino acid (except for proline, which has a secondary amino group) has a carboxyl group, a primary amino group, and a distinctive side chain ("R-group") bonded to the α-carbon atom (Figure 1.1A). At physiologic pH (approximately pH 7.4), the carboxyl group is dissociated, forming the negatively charged carboxylate ion ($-COO^-$), and the amino group is protonated ($-NH_3^+$). In proteins, almost all of these carboxyl and amino groups are combined through peptide linkage and, in general, are not available for chemical reaction except for hydrogen bond formation (Figure 1.1B). Thus, it is the nature of the side chains that ultimately dictates the role

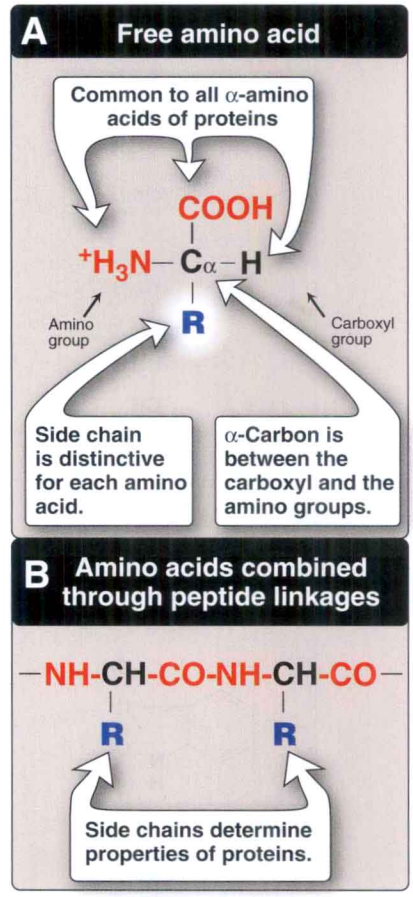


Figure 1.1
Structural features of amino acids (shown in their fully protonated form).

an amino acid plays in a protein. It is, therefore, useful to classify the amino acids according to the properties of their side chains, that is, whether they are nonpolar (have an even distribution of electrons) or polar (have an uneven distribution of electrons, such as acids and bases; Figures 1.2 and 1.3).

A. Amino acids with nonpolar side chains

Each of these amino acids has a nonpolar side chain that does not gain or lose protons or participate in hydrogen or ionic bonds (Figure 1.2). The side chains of these amino acids can be thought of as "oily" or lipid-like, a property that promotes hydrophobic interactions (see Figure 2.10, p. 19).

1. **Location of nonpolar amino acids in proteins:** In proteins found in aqueous solutions—a polar environment—the side chains of the nonpolar amino acids tend to cluster together in the interior of the protein (Figure 1.4). This phenomenon, known as the hydrophobic

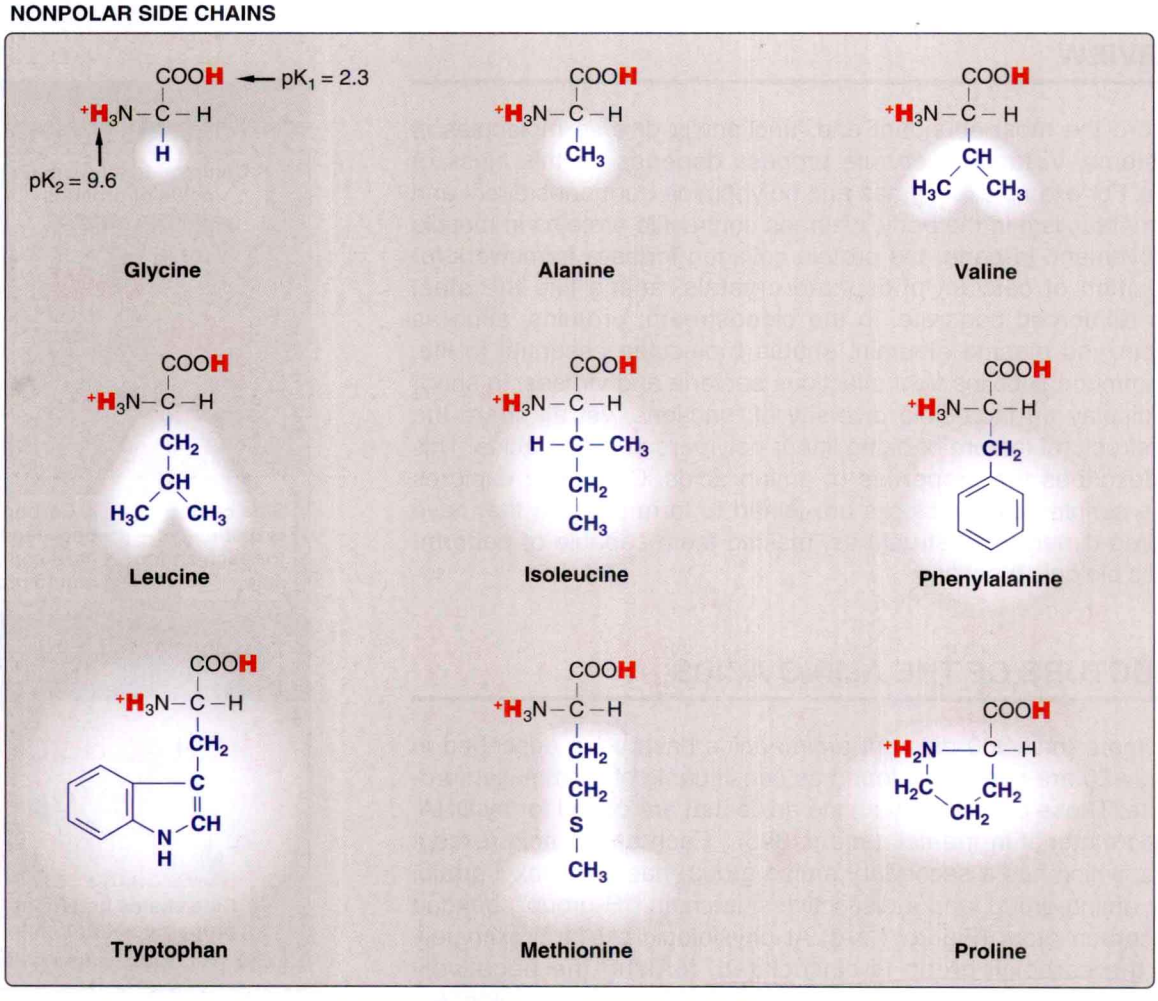


Figure 1.2
Classification of the 20 amino acids commonly found in proteins, according to the charge and polarity of their side chains at acidic pH is shown here and continues in Figure 1.3. Each amino acid is shown in its fully protonated form, with dissociable hydrogen ions represented in red print. The pK values for the α-carboxyl and α-amino groups of the nonpolar amino acids are similar to those shown for glycine. (Continued in Figure 1.3.)

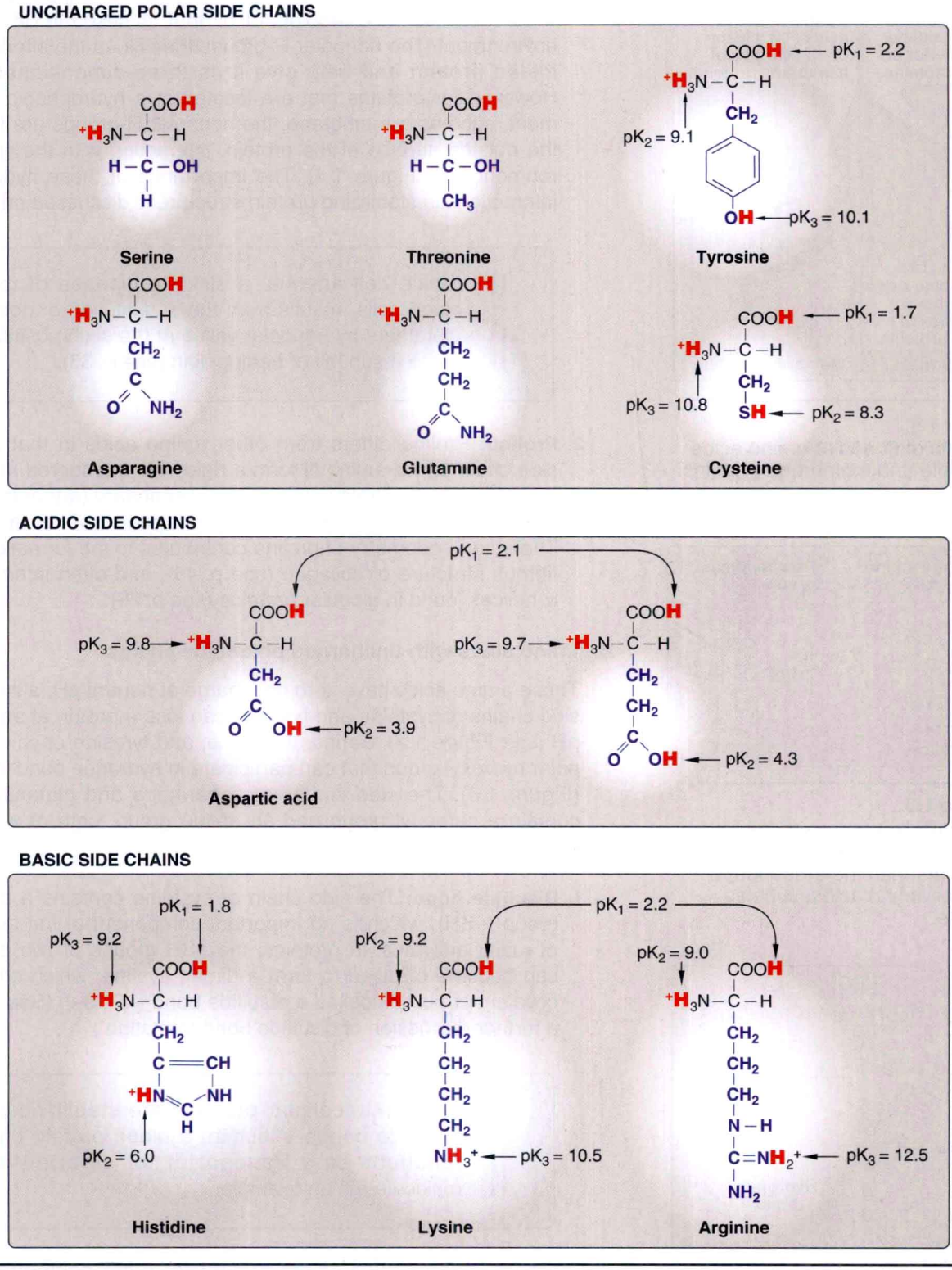


Figure 1.3
Classification of the 20 amino acids commonly found in proteins, according to the charge and polarity of their side chains at acidic pH (continued from Figure 1.2).

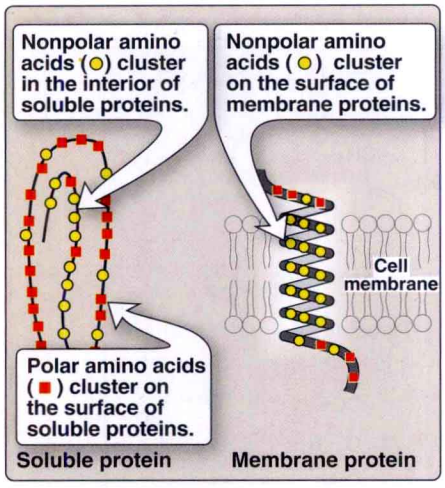


Figure 1.4
Location of nonpolar amino acids in soluble and membrane proteins.

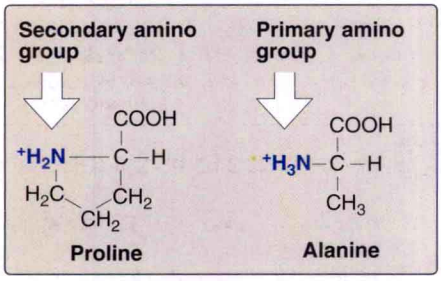


Figure 1.5
Comparison of the secondary amino group found in proline with the primary amino group found in other amino acids, such as alanine.

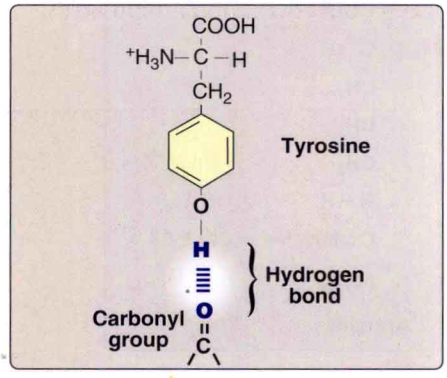


Figure 1.6
Hydrogen bond between the phenolic hydroxyl group of tyrosine and another molecule containing a carbonyl group.

effect, is the result of the hydrophobicity of the nonpolar R-groups, which act much like droplets of oil that coalesce in an aqueous environment. The nonpolar R-groups thus fill up the interior of the folded protein and help give it its three-dimensional shape. However, for proteins that are located in a hydrophobic environment, such as a membrane, the nonpolar R-groups are found on the outside surface of the protein, interacting with the lipid environment (see Figure 1.4). The importance of these hydrophobic interactions in stabilizing protein structure is discussed on p. 19.

> Sickle cell anemia, a sickling disease of red blood cells, results from the substitution of polar glutamate by nonpolar valine at the sixth position in the β subunit of hemoglobin (see p. 36).

2. **Proline:** Proline differs from other amino acids in that proline's side chain and α-amino N form a rigid, five-membered ring structure (Figure 1.5). Proline, then, has a secondary (rather than a primary) amino group. It is frequently referred to as an imino acid. The unique geometry of proline contributes to the formation of the fibrous structure of collagen (see p. 45), and often interrupts the α-helices found in globular proteins (see p. 26).

B. Amino acids with uncharged polar side chains

These amino acids have zero net charge at neutral pH, although the side chains of cysteine and tyrosine can lose a proton at an alkaline pH (see Figure 1.3). Serine, threonine, and tyrosine each contain a polar hydroxyl group that can participate in hydrogen bond formation (Figure 1.6). The side chains of asparagine and glutamine each contain a carbonyl group and an amide group, both of which can also participate in hydrogen bonds.

1. **Disulfide bond:** The side chain of cysteine contains a sulfhydryl group (–SH), which is an important component of the active site of many enzymes. In proteins, the –SH groups of two cysteines can become oxidized to form a dimer, cystine, which contains a covalent cross-link called a disulfide bond (–S–S–). (See p. 19 for a further discussion of disulfide bond formation.)

> Many extracellular proteins are stabilized by disulfide bonds. Albumin, a blood protein that functions as a transporter for a variety of molecules, is an example.

2. **Side chains as sites of attachment for other compounds:** The polar hydroxyl group of serine, threonine, and, rarely, tyrosine, can serve as a site of attachment for structures such as a phosphate group. In addition, the amide group of asparagine, as well as the hydroxyl group of serine or threonine, can serve as a site of attachment for oligosaccharide chains in glycoproteins (see p. 165).

C. Amino acids with acidic side chains

The amino acids aspartic and glutamic acid are proton donors. At physiologic pH, the side chains of these amino acids are fully ionized, containing a negatively charged carboxylate group ($-COO^-$). They are, therefore, called aspartate or glutamate to emphasize that these amino acids are negatively charged at physiologic pH (see Figure 1.3).

D. Amino acids with basic side chains

The side chains of the basic amino acids accept protons (see Figure 1.3). At physiologic pH the side chains of lysine and arginine are fully ionized and positively charged. In contrast, histidine is weakly basic, and the free amino acid is largely uncharged at physiologic pH. However, when histidine is incorporated into a protein, its side chain can be either positively charged or neutral, depending on the ionic environment provided by the polypeptide chains of the protein. This is an important property of histidine that contributes to the role it plays in the functioning of proteins such as hemoglobin (see p. 31).

E. Abbreviations and symbols for commonly occurring amino acids

Each amino acid name has an associated three-letter abbreviation and a one-letter symbol (Figure 1.7). The one-letter codes are determined by the following rules:

1. **Unique first letter:** If only one amino acid begins with a particular letter, then that letter is used as its symbol. For example, I = isoleucine.

2. **Most commonly occurring amino acids have priority:** If more than one amino acid begins with a particular letter, the most common of these amino acids receives this letter as its symbol. For example, glycine is more common than glutamate, so G = glycine.

3. **Similar sounding names:** Some one-letter symbols sound like the amino acid they represent. For example, F = phenylalanine, or W = tryptophan ("twyptophan" as Elmer Fudd would say).

4. **Letter close to initial letter:** For the remaining amino acids, a one-letter symbol is assigned that is as close in the alphabet as possible to the initial letter of the amino acid, for example, K = lysine. Furthermore, B is assigned to Asx, signifying either aspartic acid or asparagine, Z is assigned to Glx, signifying either glutamic acid or glutamine, and X is assigned to an unidentified amino acid.

F. Optical properties of amino acids

The α-carbon of an amino acid is attached to four different chemical groups and is, therefore, a chiral or optically active carbon atom. Glycine is the exception because its α-carbon has two hydrogen substituents and, therefore, is optically inactive. Amino acids that have an asymmetric center at the α-carbon can exist in two forms, designated D and L, that are mirror images of each other (Figure 1.8). The two forms in each pair are termed stereoisomers, optical isomers, or enantiomers. All amino acids found in proteins are of the L-configuration. However, D-amino acids are found in some antibiotics and in plant and bacterial cell walls. (See p. 253 for a discussion of D-amino acid metabolism.)

1 Unique first letter:

Cysteine	=	Cys	= **C**
Histidine	=	His	= **H**
Isoleucine	=	Ile	= **I**
Methionine	=	Met	= **M**
Serine	=	Ser	= **S**
Valine	=	Val	= **V**

2 Most commonly occurring amino acids have priority:

Alanine	=	Ala	= **A**
Glycine	=	Gly	= **G**
Leucine	=	Leu	= **L**
Proline	=	Pro	= **P**
Threonine	=	Thr	= **T**

3 Similar sounding names:

Arginine	= Arg	= **R**	("a**R**ginine")
Asparag**in**e	= Asn	= **N**	(contains N)
Aspartate	= Asp	= **D**	("aspar**D**ic")
Glutamate	= Glu	= **E**	("glut**E**mate")
Glutamin**e**	= Gln	= **Q**	("**Q**-tamine")
Phenylalanine	= Phe	= **F**	("**F**enylalanine")
Tyrosine	= Tyr	= **Y**	("t**Y**rosine")
Tryptophan	= Trp	= **W**	(double ring in the molecule)

4 Letter close to initial letter:

Aspartate or asparagine	=	Asx	= **B** (near A)
Glutamate or glutamine	=	Glx	= **Z**
Lysine	=	Lys	= **K** (near L)
Undetermined amino acid	=		**X**

Figure 1.7
Abbreviations and symbols for the commonly occurring amino acids.

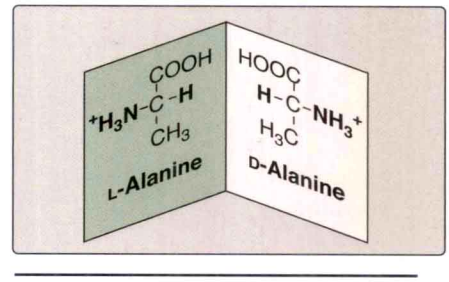


Figure 1.8
D and L forms of alanine are mirror images.

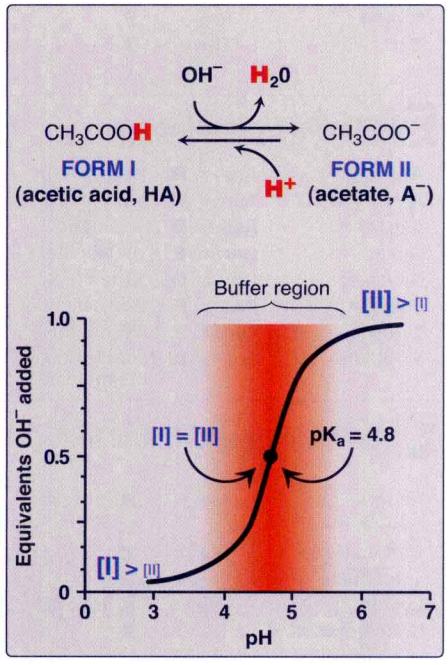


Figure 1.9
Titration curve of acetic acid.

III. ACIDIC AND BASIC PROPERTIES OF AMINO ACIDS

Amino acids in aqueous solution contain weakly acidic α-carboxyl groups and weakly basic α-amino groups. In addition, each of the acidic and basic amino acids contains an ionizable group in its side chain. Thus, both free amino acids and some amino acids combined in peptide linkages can act as buffers. Recall that acids may be defined as proton donors and bases as proton acceptors. Acids (or bases) described as "weak" ionize to only a limited extent. The concentration of protons in aqueous solution is expressed as pH, where pH = log $1/[H^+]$ or $-\log [H^+]$. The quantitative relationship between the pH of the solution and concentration of a weak acid (HA) and its conjugate base (A^-) is described by the Henderson-Hasselbalch equation.

A. Derivation of the equation

Consider the release of a proton by a weak acid represented by HA:

$$\underset{\text{weak acid}}{HA} \rightleftarrows \underset{\text{proton}}{H^+} + \underset{\text{salt form or conjugate base}}{A^-}$$

The "salt" or conjugate base, A^-, is the ionized form of a weak acid. By definition, the dissociation constant of the acid, K_a, is

$$K_a = \frac{[H^+][A^-]}{[HA]}$$

[Note: The larger the K_a, the stronger the acid, because most of the HA has dissociated into H^+ and A^-. Conversely, the smaller the K_a, the less acid has dissociated and, therefore, the weaker the acid.] By solving for the $[H^+]$ in the above equation, taking the logarithm of both sides of the equation, multiplying both sides of the equation by -1, and substituting $pH = -\log [H^+]$ and $pK_a = -\log K_a$, we obtain the Henderson-Hasselbalch equation:

$$pH = pK_a + \log \frac{[A^-]}{[HA]}$$

B. Buffers

A buffer is a solution that resists change in pH following the addition of an acid or base. A buffer can be created by mixing a weak acid (HA) with its conjugate base (A^-). If an acid such as HCl is then added to such a solution, A^- can neutralize it, in the process being converted to HA. If a base is added, HA can neutralize it, in the process being converted to A^-. Maximum buffering capacity occurs at a pH equal to the pK_a, but a conjugate acid/base pair can still serve as an effective buffer when the pH of a solution is within approximately ±1 pH unit of the pK_a. If the

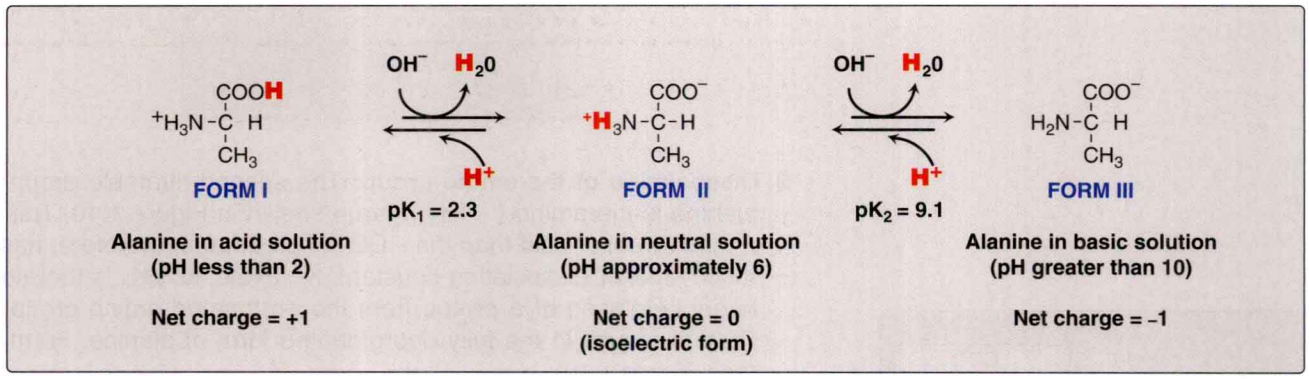


Figure 1.10
Ionic forms of alanine in acidic, neutral, and basic solutions.

amounts of HA and A^- are equal, the pH is equal to the pK_a. As shown in Figure 1.9, a solution containing acetic acid (HA = CH_3-COOH) and acetate (A^- = CH_3-COO^-) with a pK_a of 4.8 resists a change in pH from pH 3.8 to 5.8, with maximum buffering at pH 4.8. At pH values less than the pK_a, the protonated acid form (CH_3-COOH) is the predominant species. At pH values greater than the pK_a, the deprotonated base form (CH_3-COO^-) is the predominant species in solution.

C. Titration of an amino acid

1. **Dissociation of the carboxyl group:** The titration curve of an amino acid can be analyzed in the same way as described for acetic acid. Consider alanine, for example, which contains both an α-carboxyl and an α-amino group. At a low (acidic) pH, both of these groups are protonated (shown in Figure 1.10). As the pH of the solution is raised, the $-COOH$ group of Form I can dissociate by donating a proton to the medium. The release of a proton results in the formation of the carboxylate group, $-COO^-$. This structure is shown as Form II, which is the dipolar form of the molecule (see Figure 1.10). This form, also called a zwitterion, is the isoelectric form of alanine, that is, it has an overall (net) charge of zero.

2. **Application of the Henderson-Hasselbalch equation:** The dissociation constant of the carboxyl group of an amino acid is called K_1, rather than K_a, because the molecule contains a second titratable group. The Henderson-Hasselbalch equation can be used to analyze the dissociation of the carboxyl group of alanine in the same way as described for acetic acid:

$$K_1 = \frac{[H^+][II]}{[I]}$$

where I is the fully protonated form of alanine, and II is the isoelectric form of alanine (see Figure 1.10). This equation can be rearranged and converted to its logarithmic form to yield:

$$pH = pK_1 + \log \frac{[II]}{[I]}$$

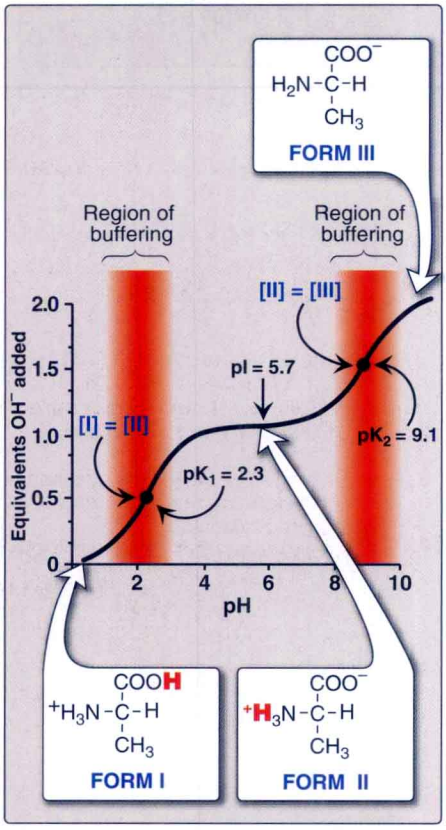


Figure 1.11
The titration curve of alanine.

3. **Dissociation of the amino group:** The second titratable group of alanine is the amino ($-NH_3^+$) group shown in Figure 1.10. This is a much weaker acid than the $-COOH$ group and, therefore, has a much smaller dissociation constant, K_2. [Note: Its pK_a is therefore larger.] Release of a proton from the protonated amino group of Form II results in the fully deprotonated form of alanine, Form III (see Figure 1.10).

4. **pKs of alanine:** The sequential dissociation of protons from the carboxyl and amino groups of alanine is summarized in Figure 1.10. Each titratable group has a pK_a that is numerically equal to the pH at which exactly one half of the protons have been removed from that group. The pK_a for the most acidic group ($-COOH$) is pK_1, whereas the pK_a for the next most acidic group ($-NH_3^+$) is pK_2.

5. **Titration curve of alanine:** By applying the Henderson-Hasselbalch equation to each dissociable acidic group, it is possible to calculate the complete titration curve of a weak acid. Figure 1.11 shows the change in pH that occurs during the addition of base to the fully protonated form of alanine (I) to produce the completely deprotonated form (III). Note the following:

   a. **Buffer pairs:** The $-COOH/-COO^-$ pair can serve as a buffer in the pH region around pK_1, and the $-NH_3^+/-NH_2$ pair can buffer in the region around pK_2.

   b. **When pH = pK:** When the pH is equal to pK_1 (2.3), equal amounts of Forms I and II of alanine exist in solution. When the pH is equal to pK_2 (9.1), equal amounts of Forms II and III are present in solution.

   c. **Isoelectric point:** At neutral pH, alanine exists predominantly as the dipolar Form II in which the amino and carboxyl groups are ionized, but the net charge is zero. The isoelectric point (pI) is the pH at which an amino acid is electrically neutral, that is, in which the sum of the positive charges equals the sum of the negative charges. For an amino acid, such as alanine, that has only two dissociable hydrogens (one from the α-carboxyl and one from the α-amino group), the pI is the average of pK_1 and pK_2 (pI = [2.3 + 9.1]/2 = 5.7, see Figure 1.11). The pI is thus midway between pK_1 (2.3) and pK_2 (9.1). pI corresponds to the pH at which the Form II (with a net charge of zero) predominates, and at which there are also equal amounts of Forms I (net charge of +1) and III (net charge of –1).

Separation of plasma proteins by charge typically is done at a pH above the pI of the major proteins, thus, the charge on the proteins is negative. In an electric field, the proteins will move toward the positive electrode at a rate determined by their net negative charge. Variations in the mobility pattern are suggestive of certain diseases.

6. **Net charge of amino acids at neutral pH:** At physiologic pH, amino acids have a negatively charged group ($-COO^-$) and a positively charged group ($-NH_3^+$), both attached to the α-carbon. [Note: Glutamate, aspartate, histidine, arginine, and lysine have additional potentially charged groups in their side chains.] Substances, such as amino acids, that can act either as an acid or a base are defined as amphoteric, and are referred to as ampholytes (amphoteric electrolytes).

D. Other applications of the Henderson-Hasselbalch equation

The Henderson-Hasselbalch equation can be used to calculate how the pH of a physiologic solution responds to changes in the concentration of a weak acid and/or its corresponding "salt" form. For example, in the bicarbonate buffer system, the Henderson-Hasselbalch equation predicts how shifts in the bicarbonate ion concentration, $[HCO_3^-]$, and CO_2 influence pH (Figure 1.12A). The equation is also useful for calculating the abundance of ionic forms of acidic and basic drugs. For example, most drugs are either weak acids or weak bases (Figure 1.12B). Acidic drugs (HA) release a proton (H^+), causing a charged anion (A^-) to form.

$$HA \rightleftarrows H^+ + A^-$$

Weak bases (BH^+) can also release a H^+. However, the protonated form of basic drugs is usually charged, and the loss of a proton produces the uncharged base (B).

$$BH^+ \rightleftarrows B + H^+$$

A drug passes through membranes more readily if it is uncharged. Thus, for a weak acid such as aspirin, the uncharged HA can permeate through membranes and A^- cannot. For a weak base, such as morphine, the uncharged form, B, penetrates through the cell membrane and BH^+ does not. Therefore, the effective concentration of the permeable form of each drug at its absorption site is determined by the relative concentrations of the charged and uncharged forms. The ratio between the two forms is determined by the pH at the site of absorption, and by the strength of the weak acid or base, which is represented by the pK_a of the ionizable group. The Henderson-Hasselbalch equation is useful in determining how much drug is found on either side of a membrane that separates two compartments that differ in pH, for example, the stomach (pH 1.0–1.5) and blood plasma (pH 7.4).

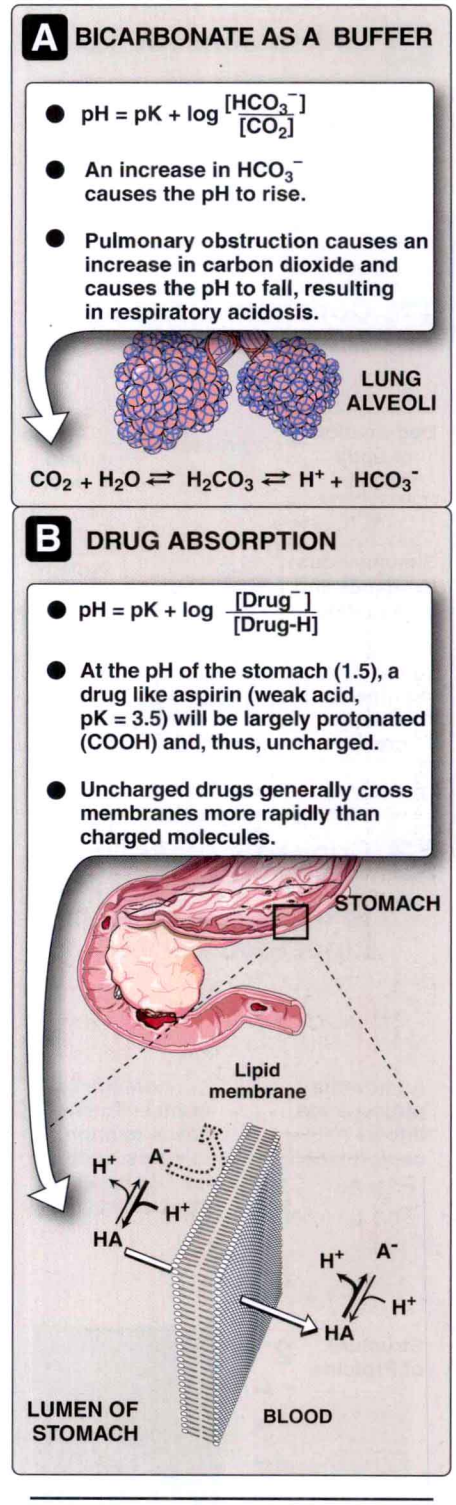


Figure 1.12
The Henderson-Hasselbalch equation is used to predict: A, changes in pH as the concentrations of HCO_3^- or CO_2 are altered; or B, the ionic forms of drugs.

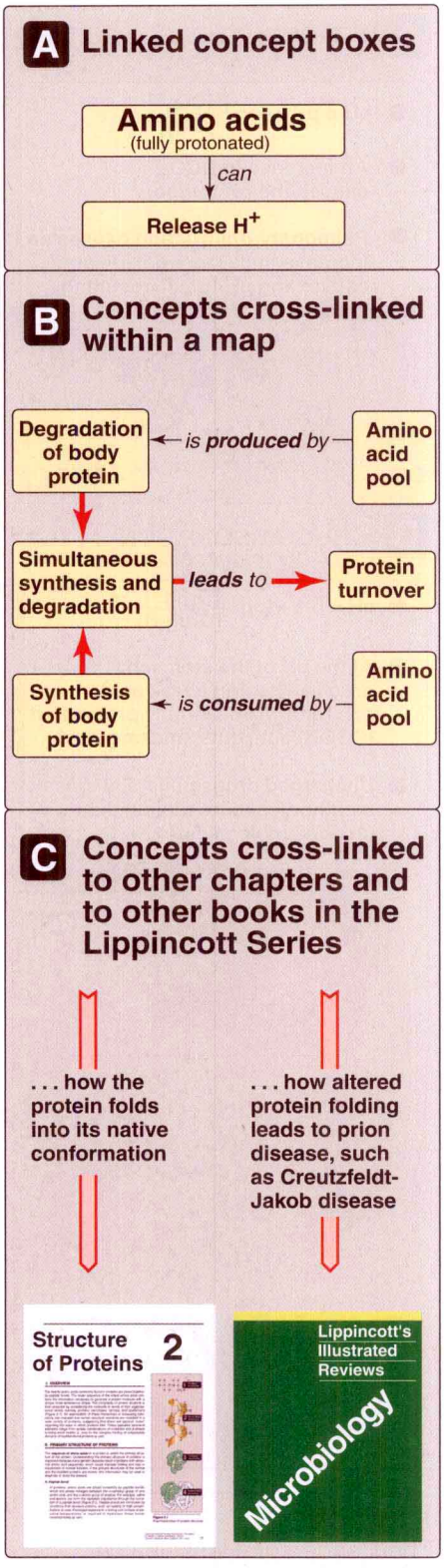


Figure 1.13
Symbols used in concept maps.

IV. CONCEPT MAPS

Students sometimes view biochemistry as a blur of facts or equations to be memorized, rather than a body of concepts to be understood. Details provided to enrich understanding of these concepts inadvertently turn into distractions. What seems to be missing is a road map—a guide that provides the student with an intuitive understanding of how various topics fit together to make sense. The authors have, therefore, created a series of biochemical concept maps to graphically illustrate relationships between ideas presented in a chapter, and to show how the information can be grouped or organized. A concept map is, thus, a tool for visualizing the connections between concepts. Material is represented in a hierarchic fashion, with the most inclusive, most general concepts at the top of the map, and the more specific, less general concepts arranged beneath. The concept maps ideally function as templates or guides for organizing information, so the student can readily find the best ways to integrate new information into knowledge they already possess.

A. How is a concept map constructed?

1. **Concept boxes and links:** Educators define concepts as "perceived regularities in events or objects." In our biochemical maps, concepts include abstractions (for example, free energy), processes (for example, oxidative phosphorylation), and compounds (for example, glucose 6-phosphate). These broadly defined concepts are prioritized with the central idea positioned at the top of the page. The concepts that follow from this central idea are then drawn in boxes (Figure 1.13A). The size of the type indicates the relative importance of each idea. Lines are drawn between concept boxes to show which are related. The label on the line defines the relationship between two concepts, so that it reads as a valid statement, that is, the connection creates meaning. The lines with arrowheads indicate in which direction the connection should be read (Figure 1.14).

2. **Cross-links:** Unlike linear flow charts or outlines, concept maps may contain cross-links that allow the reader to visualize complex relationships between ideas represented in different parts of the map (Figure 1.13B), or between the map and other chapters in this book or companion books in the series (Figure 1.13C). Cross-links can thus identify concepts that are central to more than one discipline, empowering students to be effective in clinical situations, and on the United States Medical Licensure Examination (USMLE) or other examinations, that bridge disciplinary boundaries. Students learn to visually perceive nonlinear relationships between facts, in contrast to cross-referencing within linear text.

V. CHAPTER SUMMARY

Each amino acid has an **α-carboxyl group** and a primary **α-amino group** (except for proline, which has a **secondary amino group**). At physiologic pH, the α-carboxyl group is dissociated, forming the negatively charged carboxylate ion ($-COO^-$), and the α-amino group is protonated ($-NH_3^+$). Each amino acid also contains one of 20 distinctive

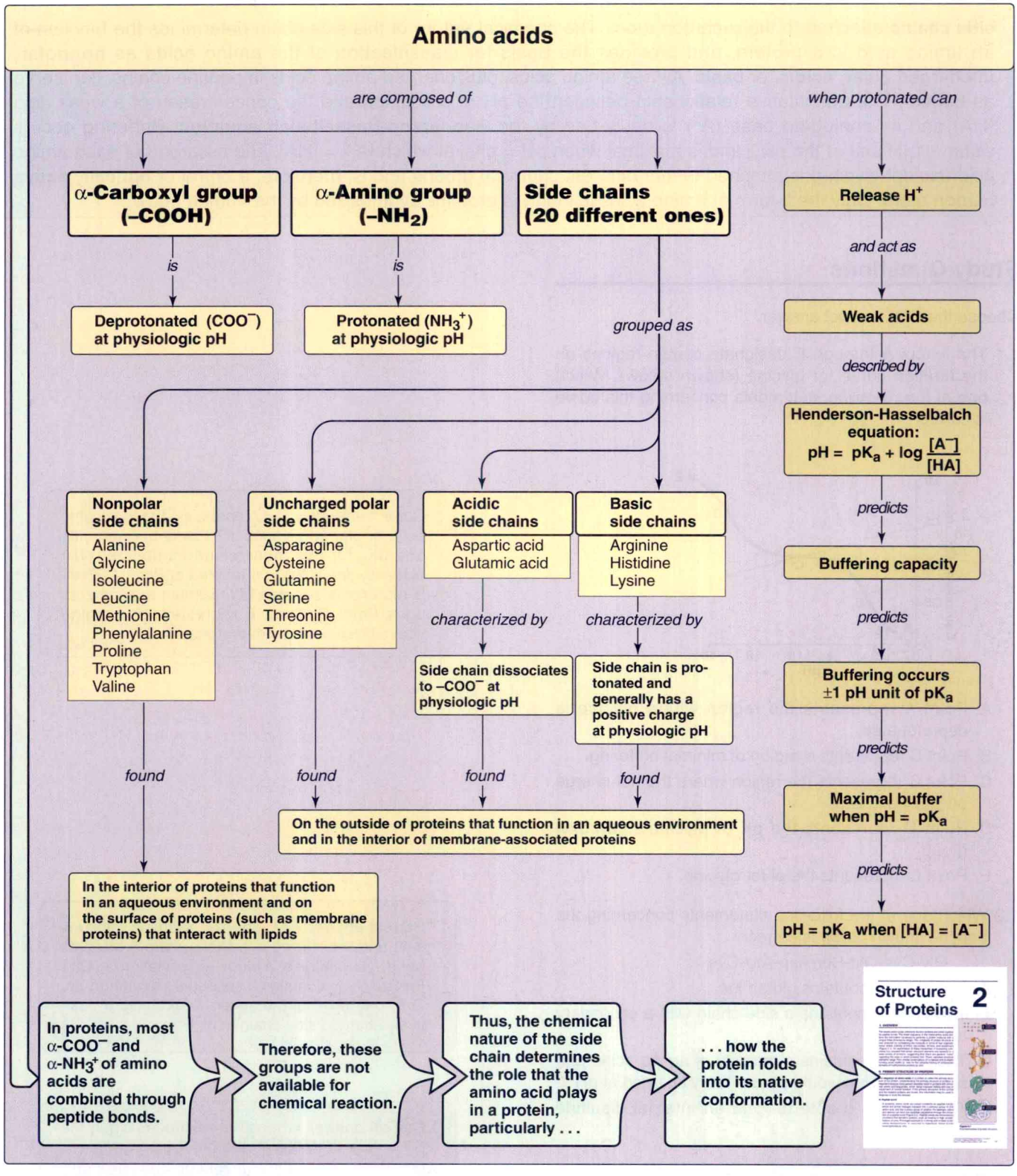


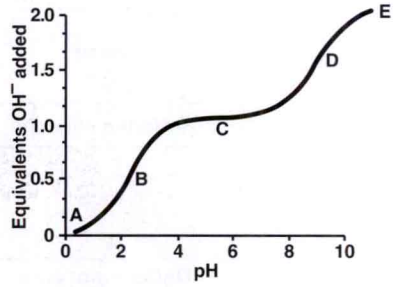
Figure 1.14
Key concept map for amino acids.

side chains attached to the α-carbon atom. The chemical nature of this side chain determines the function of an amino acid in a protein, and provides the basis for classification of the amino acids as **nonpolar**, **uncharged polar**, **acidic**, or **basic**. All free amino acids, plus charged amino acids in peptide chains, can serve as **buffers**. The quantitative relationship between the pH of a solution and the concentration of a weak acid (HA) and its conjugate base (A^-) is described by the **Henderson-Hasselbalch equation**. Buffering occurs within ±1pH unit of the pK_a, and is maximal when pH = pK_a, at which $[A^-] = [HA]$. The α-carbon of each amino acid (except glycine) is attached to four different chemical groups and is, therefore, a **chiral** or **optically active** carbon atom. Only the L-form of amino acids is found in proteins synthesized by the human body.

Study Questions

Choose the ONE correct answer.

1.1 The letters A through E designate certain regions on the titration curve for glycine (shown below). Which one of the following statements concerning this curve is correct?



A. Point A represents the region where glycine is deprotonated.
B. Point B represents a region of minimal buffering.
C. Point C represents the region where the net charge on glycine is zero.
D. Point D represents the pK of glycine's carboxyl group.
E. Point E represents the pI for glycine.

Correct answer = C. C represents the isoelectric point or pI, and as such is midway between pK_1 and pK_2 for this monoamino monocarboxylic acid. Glycine is fully protonated at Point A. Point B represents a region of maximum buffering, as does Point D. Point E represents the region where glycine is fully deprotonated.

1.2 Which one of the following statements concerning the peptide shown below is correct?

Gly-Cys-Glu-Ser-Asp-Arg-Cys

A. The peptide contains glutamine.
B. The peptide contains a side chain with a secondary amino group.
C. The peptide contains a majority of amino acids with side chains that would be positively charged at pH 7.
D. The peptide is able to form an internal disulfide bond.

Correct answer = D. The two cysteine residues can, under oxidizing conditions, form a disulfide bond. Glutamine's 3-letter abbreviation is Gln. Proline (Pro) contains a secondary amino group. Only one (Arg) of the seven would have a positively charged side chain at pH 7.

1.3 Given that the pI for glycine is 6.1, to which electrode, positive or negative, will glycine move in an electric field at pH 2? Explain.

Correct answer = negative electrode. When the pH is less than the pI, the charge on glycine is positive because the α-amino group is fully protonated. (Recall that glycine has H as its R group).

Structure of Proteins

2

I. OVERVIEW

The 20 amino acids commonly found in proteins are joined together by peptide bonds. The linear sequence of the linked amino acids contains the information necessary to generate a protein molecule with a unique three-dimensional shape. The complexity of protein structure is best analyzed by considering the molecule in terms of four organizational levels, namely, primary, secondary, tertiary, and quaternary (Figure 2.1). An examination of these hierarchies of increasing complexity has revealed that certain structural elements are repeated in a wide variety of proteins, suggesting that there are general "rules" regarding the ways in which proteins achieve their native, functional form. These repeated structural elements range from simple combinations of α-helices and β–sheets forming small motifs, to the complex folding of polypeptide domains of multifunctional proteins (see p. 18).

II. PRIMARY STRUCTURE OF PROTEINS

The sequence of amino acids in a protein is called the primary structure of the protein. Understanding the primary structure of proteins is important because many genetic diseases result in proteins with abnormal amino acid sequences, which cause improper folding and loss or impairment of normal function. If the primary structures of the normal and the mutated proteins are known, this information may be used to diagnose or study the disease.

A. Peptide bond

In proteins, amino acids are joined covalently by peptide bonds, which are amide linkages between the α-carboxyl group of one amino acid and the α-amino group of another. For example, valine and alanine can form the dipeptide valylalanine through the formation of a peptide bond (Figure 2.2). Peptide bonds are not broken by conditions that denature proteins, such as heating or high concentrations of urea (see p. 20). Prolonged exposure to a strong acid or base at elevated temperatures is required to hydrolyze these bonds nonenzymically.

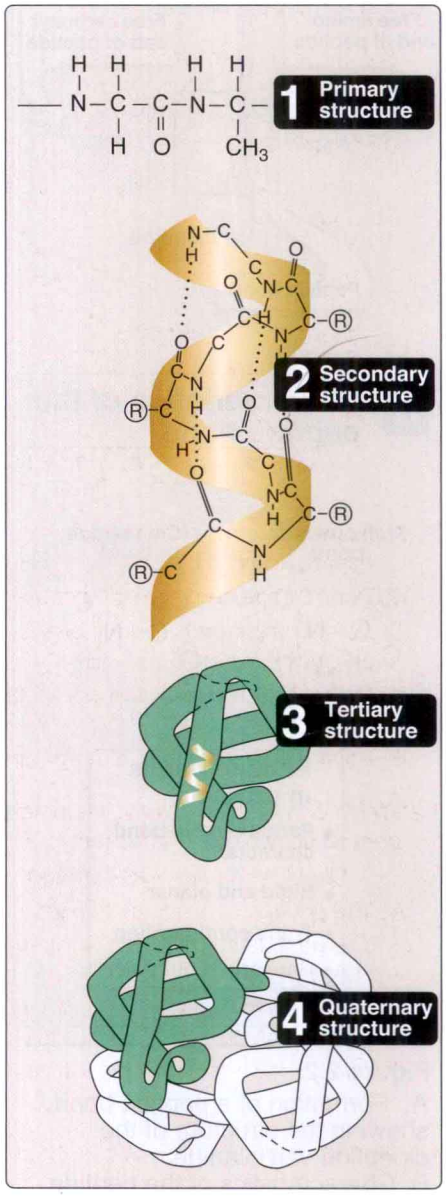


Figure 2.1
Four hierarchies of protein structure.